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Authors

Tan, Nelly
Shen, Luyao
Khoshnoodi, Pooria
et al.

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Pathological and 3 Tesla Volumetric Magnetic Resonance Imaging Predictors of Biochemical Recurrence after Robotic Assisted Radical Prostatectomy: Correlation with Whole Mount Histopathology

Nelly Tan[*,†], **Luyao Shen**[†], **Pooria Khoshnoodi**, **Héctor E. Alcalá**, **Weixia Yu**, **William Hsu**, **Robert E. Reiter**, **David Y. Lu**, **Steven S. Raman**

School of Medicine University of California-Riverside (NT), Riverside, Department of Radiology, Loma Linda University (NT, WH, SSR), Loma Linda and Departments of Radiological Sciences (LS, PK), Urology (RER) and Pathology (DYL) and Computing Technology Research Laboratory, David Geffen School of Medicine (WY), University of California-Los Angeles, Los Angeles, California, and Department of Family, Population and Preventive Medicine, Stony Brook University (HEA), Stony Brook, New York

Abstract

Purpose: We sought to identify the clinical and magnetic resonance imaging variables predictive of biochemical recurrence after robotic assisted radical prostatectomy in patients who underwent multiparametric 3 Tesla prostate magnetic resonance imaging.

Materials and Methods: We performed an institutional review board approved, HIPAA (Health Insurance Portability and Accountability Act) compliant, single arm observational study of 3 Tesla multiparametric magnetic resonance imaging prior to robotic assisted radical prostatectomy from December 2009 to March 2016. Clinical, magnetic resonance imaging and pathological information, and clinical outcomes were compiled. Biochemical recurrence was defined as prostate specific antigen 0.2 ng/cc or greater. Univariate and multivariate regression analysis was performed.

Results: Biochemical recurrence had developed in 62 of the 255 men (24.3%) included in the study at a median followup of 23.5 months. Compared to the subcohort without biochemical recurrence the subcohort with biochemical recurrence had a greater proportion of patients with a high grade biopsy Gleason score, higher preoperative prostate specific antigen (7.4 vs 5.6 ng/ml), intermediate and high D'Amico classifications, larger tumor volume on magnetic resonance imaging (0.66 vs 0.30 ml), higher PI-RADS® (Prostate Imaging-Reporting and Data System) version 2 category lesions, a greater proportion of intermediate and high grade radical prostatectomy Gleason score lesions, higher pathological T3 stage (all $p < 0.01$) and a higher positive surgical margin rate (19.3% vs 7.8%, $p = 0.016$). On multivariable analysis only tumor volume on magnetic resonance imaging (adjusted OR 1.57, $p = 0.016$), pathological T stage

[*]Correspondence: University of California-Riverside, Riverside, California (telephone: 310-957-9021; nelly.tan@ucr.edu).
[†]Equal study contribution.

(adjusted OR 2.26, p = 0.02), positive surgical margin (adjusted OR 5.0, p = 0.004) and radical prostatectomy Gleason score (adjusted OR 2.29, p = 0.004) predicted biochemical recurrence.

Conclusions: In this cohort tumor volume on magnetic resonance imaging and pathological variables, including Gleason score, staging and positive surgical margins, significantly predicted biochemical recurrence. This suggests an important new imaging biomarker.

Keywords

prostatic neoplasms; neoplasm recurrence; local; prostate specific antigen; magnetic resonance imaging; biomarkers; tumor

PROSTATE cancer is the second leading cause of cancer death in men in the United States.[1] Although localized PCa can be definitively treated with RALP, as many as 30% of patients can experience BCR after RALP.[2,3] Various nomograms have been developed to predict BCR after surgery using established preoperative clinical variables such as PSA, biopsy Gleason score and digital rectal examination.[4,5] However, most existing nomograms lack the anatomical and functional information provided by imaging.

As a powerful imaging tool for diagnosis, staging, image guided biopsy and preoperative planning 3TmpMRI has emerged.[6–8] It can provide anatomical, functional and 3D information (ie volumetric data),[9] which is increasingly used to augment existing clinical models to offer improved predictions of biochemical recurrence. Existing studies to date have emphasized qualitative instead of quantitative features,[10] did not use whole mount pathology as a reference standard,[10] used length based measurement such as tumor contact length[11] or studied patients using 1.5 Tesla[12] instead of 3 Tesla MRI.

To our knowledge no studies have evaluated the usefulness of contemporary 3D MRI data (ie 3D MRI volume) and the newer standardized PI-RADS® v2 lexicon combined with state-of-the-art 3TmpMRI to evaluate for biochemical recurrence using whole mount pathology and postoperative PSA as standard references. Therefore, the purpose of this study was to investigate clinical, 3D and conventional quantitative 3TmpMRI predictors using whole mount histopathology as the ground truth to predict BCR after RALP.

METHODS

Study Design

After institutional review board approval and in compliance with the 1996 HIPAA (Health Insurance Portability and Accountability Act) we performed a single arm, observational, single institution study of 395 consecutive patients who underwent 3TmpMRI of the prostate prior to RALP between December 2009 and March 2016. Of the 395 patients 140 lacked followup postoperative PSA and were excluded from analysis. The final study cohort comprised 255 consecutive patients with followup postoperative PSA.

Clinical Information

We collected clinical data (preoperative biopsy Gleason score, patient age and preoperative PSA), MRI information (tumor diameter and volume, prostate volume, solitary vs multifocal

tumor, cancer location and PI-RADS v2 category), radical prostatectomy information (Gleason score, pathological stage and positive surgical margins) and clinical outcomes (biochemical recurrence and followup). Biochemical recurrence was defined as postoperative PSA 0.2 ng/ml or greater with an additional PSA 0.2 ng/ml or greater for confirmation when available.[12] The index tumor was defined as the lesion with the highest radical prostatectomy Gleason score on whole mount histopathology. If the patient had a multifocal tumor with the same Gleason score, the tumor with the longest diameter served as the index lesion. Patients were categorized at low, intermediate or high risk according to the standard D'Amico classification.[13]

Magnetic Resonance Imaging

We performed 3TmpMRI using an endorectal coil (MedRAD®) and an external phased array on 1 of several 3 Tesla magnets, including a Trio, Verio or Skyra for 3.0 (Siemens®), in 180 of the 255 patients (70.6%). The remainder underwent external phased array coil mpMRI alone.

The 3TmpMRI protocol included conventional T2W, diffusion-weighted imaging and dynamic contrast enhanced sequences. Images were reviewed with DynaCAD 3 (Philips Invivo®) for 3-dimensional volume of interest delineation of prostate and tumor volumes on T2W. The MRI tumor was contoured on every slice on T2W images and volume was subsequently generated by the software. For all MRI lesions tumor volume was calculated at the time of MRI interpretation by the radiologist. This information was available for referring providers before radical prostatectomy.

Multiparametric Magnetic Resonance Imaging, and Histopathological Analysis and Correlation

Images were interpreted by a single reader, that is 1 of 2 fellowship trained genitourinary radiologists (DJM or SSR) with 8 and 15 years of experience with prostate MRI, respectively. They prospectively identified PCa on preoperative mpMRI. Lesions were then characterized for aggressiveness with PI-RADS v2.[13]

WMHP was analyzed by 1 of 2 dedicated genitourinary pathologists (JH or DYL) with 15 and 4 years of experience with prostate pathology, respectively, while blinded to MRI information. On each section for each individual PCa focus we recorded lesion size, diagrammatic location and Gleason score. In a series of monthly joint sessions 3TmpMRI findings were initially rereviewed and all MRI detected lesions were matched by at least 1 genitourinary radiologist (DJM and/or SSR) with their counterparts on WMHP by at least 1 genitourinary pathologist (DYL and/or JH).

Statistical Analysis

The median and IQR are provided. Differences in continuous variables were measured with the Mann-Whitney U test and categorical variables were measured with the chi-square or the Fisher exact test. Variables significant on univariate analysis were then used in multivariable linear regression. Of the 255 tumors 54 (21.2%) which were invisible on MRI were excluded from logistic regression and the remaining 201 were analyzed. Simple and adjusted ORs

with the 95% CI are provided. All statistical tests were performed on Stata®, version 12.1 with $p < 0.05$ considered significant.

RESULTS

Median tumor volume was 0.72 ml (IQR 0.18–0.89) on 3TmpMRI. In 62.8% and 37.2% of the patients MRI was performed for preoperative staging and planning for targeted biopsy, respectively. BCR developed in 62 of the 225 patients (24.3%). Median PSA followup in patients with and without biochemical recurrence was 36.9 and 19.5 months, respectively. Most patients had Gleason 7 PCa on biopsy, and pathological stage 2 and 3 tumors at RALP (table 1). The false-positive MRI rate (a radiological index lesion without a corresponding pathological tumor focus) was 10.6%, yielding a MRI positive predictive value of 89.4%. The false-negative rate (radical prostatectomy index tumors not seen on MRI) was 21.2%, yielding 78.8% sensitivity.

When analyzing differences in clinical and MRI parameters between the BCR and nonBCR subcohorts, we detected a significantly higher proportion of preoperatively high grade biopsy Gleason scores, higher PSA (7.4 vs 5.6 ng/ml), a higher proportion of D'Amico intermediate and high grade risk, larger 3TmpMRI tumor volume (0.66 vs 0.30 cc), a higher proportion of PI-RADS v2 category, higher pathological Gleason scores and a higher proportion of T3 stage (all $p < 0.01$) as well as a higher proportion of positive surgical margins on RALP (19.3% vs 7.8%, $p = 0.016$) in the BCR subcohort (table 2).

On multivariable logistic regression only 4 variables were significant predictors of BCR, including MRI tumor volume (adjusted OR 1.57, $p = 0.016$), post-RALP pathological stage (adjusted OR 2.3, $p = 0.02$), positive surgical margin (adjusted OR 5.0, $p = 0.004$) and pathological Gleason score (adjusted OR 2.3, $p = 0.004$, table 3). D'Amico risk classification ($p = 0.34$) and PI-RADS v2 category ($p = 0.96$) did not predict BCR in the multivariable model.

DISCUSSION

In this study we found for the first time to our knowledge that tumor volume on 3TmpMRI was the only nonpathological independent biomarker predicting BCR after RALP, in addition to previously reported postoperative pathological variables such as positive surgical margins, pathological T stage and pathological Gleason score on multivariate analysis. Further, we were unable to confirm the usefulness of previously reported clinical variables to predict BCR, such as PSA level, D'Amico risk classification and biopsy Gleason score, on multivariate analysis.[5,12,14]

To enable standardized interpretation an expert consensus document sponsored by ESUR (European Society of Urogenital Radiology) and ACR® (American College of Radiology) called PI-RADS was introduced. The initial version of PI-RADS (version 1) was published in 2012 and an update, PI-RADS v2, was published in December 2014. The diagnostic performance of PI-RADS v2 in the setting of 3TmpMRI to predict BCR has not previously been reported to our knowledge.

Our study shows that in a univariate model there were differences in PI-RADS v2 categories between the BCR and nonBCR cohorts with BCR seen in a higher proportion of PI-RADS v2 category 4 and 5 cases. However, in the multivariable model PI-RADS v2 category was not a significant predictor. PI-RADS v2 provides a standardized lexicon to interpret prostate mpMRI and stratify the malignant potential of individual lesions detected on mpMRI. It has been effective to risk stratify the detection and localization of suspicious lesions. However, our results suggest that in its current form its role for predicting BCR may be limited.

Considering the emerging role of 3TmpMRI in the improved detection, localization, staging and assessment of PCa aggressiveness for biopsy and surgical planning, several groups have investigated the usefulness of qualitative MRI to predict BCR after radical prostatectomy.[12,15–17] Although Rosenkrantz et al found that MRI tumor volume was a significant predictor of BCR in a univariate model, ADC tumor volume was not significant in a multivariable model incorporating 8 other covariates.[18] Our study demonstrated that tumor volume was a significant predictor on univariate and multivariable analyses.

The difference between the results of our study and those of Rosenkrantz et al[18] was likely due to how tumor volume was generated. we used T2W sequencing instead of ADC sequencing to generate tumor volume. T2W sequencing has higher anatomical spatial resolution than ADC, which may explain the differences in the study results. In addition, our study population was larger (255 vs 193 patients) and more patients had BCR (24.3% vs 16.6%). Thus, our series was possibly better powered to detect a difference. Despite the differences in technique as well as statistical modeling each study suggests the value of tumor volume.

Given the high accuracy of 3D prostate volume, which can be incorporated into the clinical work-flow,[9,19] the potential to measure tumor volume as well may permit improved risk stratification in patients at risk for BCR. Although the role of MRI tumor volume should be studied further, we believe that MRI tumor volume may have roles similar to those of positive biopsy core length and the percent of positive cores for understanding the tumor burden when counseling patients and discussing management. Provided that the false-positive rate of MRI is 10.6% and the corresponding positive predictive value of MRI to identify the radiological index lesion is 89.4%, we believe that MRI may provide an alternative noninvasive surrogate marker of the tumor burden to correspond with pathology findings in most but not all cases.

Park et al reported that an apparent tumor presence combined with T2W, diffusion-weighted imaging and dynamic contrast enhanced pretreatment MRI (defined as tumor visibility on diffusion-weighted imaging and dynamic contrast enhanced MRI) were significant predictors of BCR after radical prostatectomy on univariate but not multivariate analysis.[10] However, Park et al did not evaluate qualitative parameters such as the PI-RADS v2 score or quantitative parameters, or 3D data such as tumor volume in that study as we have done. To our knowledge we report one of the few studies to evaluate quantitative clinical and 3TmpMRI parameters, including 3D prostate volume.

There are several limitations to our study. 1) This was a retrospective study and subject to selection bias. Independent and prospective validation is required to confirm the findings. 2) This single institution study at a high volume, tertiary care institution with multidisciplinary expertise may not be generalizable to the general population across practices. 3) Followup was relatively short at a median of 23.5 months. 4) Results may not be applicable to MRI invisible tumors, such as cribriform tumors.[20]

Despite these limitations to our knowledge this is the largest study of 3TmpMRI using PI-RADS v2 qualitative lesion based analysis and quantitative 3D imaging parameters with WMHP correlation.

CONCLUSIONS

Our study revealed that MRI tumor volume was the only imaging variable in addition to pathological information (Gleason score, staging and positive surgical margins) which was significantly associated with higher biochemical recurrence. In addition to the other roles of MRI, including prostate cancer detection, localization and treatment planning, volumetric prostate tumor data provided by MRI may also be useful to identify patients at risk for biochemical recurrence.

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Abbreviations and Acronyms

3D	3-dimensional
3TmpMRI	3 Tesla prostate mpMRI
ADC	apparent diffusion coefficient
BCR	biochemical recurrence
mpMRI	multiparametric MRI
MRI	magnetic resonance imaging
PCa	prostate cancer
PI-RADS®	Prostate Imaging-Reporting and Data System
PSA	prostate specific antigen
RALP	robotic assisted laparoscopic radical prostatectomy
T2W	T2-weighted imaging
v2	version 2
WMHP	whole mount thin section histopathology

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Table 1.

Patient demographics

No. pts *	255	
No. 3.0 Tesla (%)	249	(97.6)
No. Biopsy Gleason score (%):	255	
No biopsy	1	(0.4)
3 + 3	72	(28.2)
3 + 4	97	(38.0)
4 + 3	27	(10.6)
8–10	58	(22.7)
Median age at surgery (IQR)	62.1	(56.8–67.5)
No. endorectal coil (%)	180	(70.6)
Median ng/ml preop PSA (IQR)	6.0	(4.7–8.3)
Median MRI tumor (IQR):		
Diameter (cm)	1.4	(1–1.8)
Vol (ml)	0.72	(0.18–0.89)
Median ml MRI prostate vol (IQR)	37	(29–47.2)
No. BCR (%):		
No	193	(75.7)
Yes	62	(24.3)
Median mos followup (IQR): †		
Overall	23.5	(9.1–43.1)
BCR	36.9	(17.6–50.2)
No BCR	19.5	(6.3–36.6)
No. prostatectomy Gleason score (%):	255	
3 + 3	34	(13.3)
3 + 4	133	(52.2)
4 + 3	53	(20.8)
8–10	35	(13.7)
No. prostatectomy index lesion stage (%):	255	
pT2	163	(63.9)
pT3a	74	(29.0)
pT3b	18	(7.1)
No. surgical margin (%):	255	
Neg	228	(89.4)
Pos	27	(10.6)

* Index tumors.

† BCR in 62 patients and no BCR in 193.

Table 2.

Clinical and MRI differences between cohorts

	Overall	No BCR		BCR		p Value
No. pts	255	193		62		–
No. biopsy Gleason score/total No. (%):						<0.01
6 or Less	73	66/73	(90.4)	7/73	(0.6)	
3 + 4	97	81/97	(83.5)	16/97	(16.5)	
4 + 3	27	14/27	(51.9)	13/27	(48.1)	
8–10	58	32/58	(55.2)	26/58	(44.8)	
Median ng/ml preop PSA (IQR)	–	5.6	(4.7–7.5)	7.4	(5.8–9.6)	<0.01
No. D'Amico classification/total No. (%):	254	192/254	(25.6)	62/254	(24.4)	<0.01
Low	67	61/67	(91.0)	6/67	(8.9)	
Intermediate	121	93/121	(76.9)	28/121	(23.1)	
High	66	38/66	(57.6)	28/66	(42.4)	
Median ml vol (IQR):						
Prostate		37	(29.3–47)	38	(25–48)	0.93
Tumor		0.30	J0.15–0.61)	0.66	(0.26–2.67)	<0.01
No. overall PI-RADS v2 category/total No. (%):		193		62		<0.01
Missed on MRI	54	43/193	(22.3)	11/62	(70.7)	
2	10	9/193	(4.7)	1/62	(1.6)	
3	38	34/193	(17.6)	4/62	(6.4)	
4	97	79/193	(40.9)	18/62	(29.0)	
5	56	28/193	(14.5)	28/62	(45.2)	
Median cm pathological tumor diameter (IQR)	–	1.9	(1.3–2.4)	2.45	(1.8–3.2)	<0.01
No. radical prostatectomy Gleason score/total No. (%):	255	193		62		<0.01
6 or Less	34	31/34	(91.2)	3/34	(8.8)	
3 + 4	133	113/133	(85.0)	20/133	(15.0)	
4 + 3	53	33/53	(62.3)	20/53	(37.7)	
8–10	35	16/35	(45.7)	19/35	(54.2)	
No. pathology stage/total No. (%):	255	193		62		<0.01
pT2	163	143/193	(74.1)	20/62	(32.3)	

	Overall	No BCR		BCR		p Value
pT3a	74	43/193	(22.3)	31/62	(50.0)	
pT3b	18	7/193	(3.6)	11/62	(70.7)	
No. surgical margin/total No. (%):	255	193		62		0.016
Neg	228	178/193	(92.2)	50/62	(80.6)	
Pos	27	15/193	(7.8)	12/62	(19.3)	

Table 3.

Logistic regression predicting prostate cancer recurrence

	OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
D'Amico score	2.76 (1.63–4.67)	<0.001	1.40 (0.70–2.81)	0.34
MRI tumor vol	1.71 (1.27–2.28)	<0.001	1.57 (1.08–2.28)	0.016
Overall PI-RADS v2 category	2.69 (1.61–4.49)	<0.001	0.98 (0.51–1.88)	0.96
Pathological stage	4.33 (2.45–7.65)	<0.001	2.26 (1.13–4.52)	0.02
Pos surgical margin	4.21 (1.65–10.71)	0.003	5.00 (1.67–14.97)	0.004
Pathological Gleason score	2.94 (1.92–4.49)	<0.001	2.29 (1.9–4.06)	0.004